

CORRECTED VERSION

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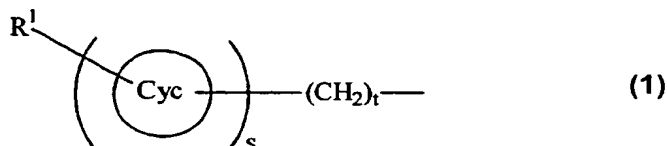
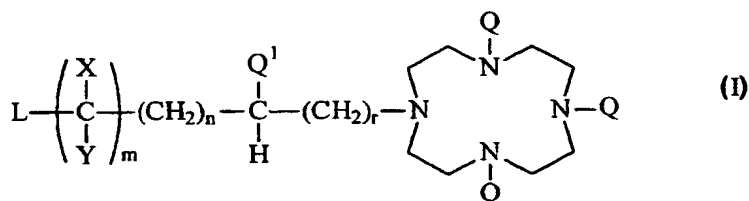
(30) Priority Data:
60/185,220 25 February 2000 (25.02.2000) US

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zosport Boulevard, Freeport, TX 77541 (US).(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CZ, DE,
DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,
ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT,
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TZ, UA, UG, US, UZ, YU, ZA, ZW.(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian

[Continued on next page]

(54) Title: ACTINIUM-225 COMPLEXES AND CONJUGATES FOR RADIOIMMUNOTHERAPY



(57) **Abstract:** Actinium-225 (²²⁵Ac) complexes with functionalized chelants of the formula (I) wherein: each Q is independently hydrogen or (CHR⁵)_pCO₂R; Q¹ is hydrogen or (CHR⁵)_wCO₂R; each R independently is hydrogen, benzyl or C₁-C₄ alkyl; with the proviso that at least two of the sum of Q and Q¹ must be other than hydrogen; each R⁵ independently is hydrogen; C₁-C₄ alkyl or (C₁-C₂ alkyl)phenyl; X and Y are each independently hydrogen or may be taken with an adjacent X and Y to form an additional carbon-carbon bond; n is 0 or 1; m is an integer from 0 to 10 inclusive; p is 1 or 2; r is 0 or 1; w is 0 or 1; with the proviso that n is only 1 when X and/or Y form an additional carbon to carbon bond, and the sum of r and w is 0 or 1; L is a linker/spacer group covalently bonded to, and replaces one hydrogen atom of one of the carbon atoms to which it is joined, said linker/spacer group being represented by the formula (1) wherein s is an integer of 0 or 1; t is an integer of 0 to 20 inclusive; R¹ is an electrophilic or nucleophilic moiety which allows for covalent attachment to an antibody or fragment thereof, or synthetic linker which can be attached to an antibody or fragment thereof, or precursor thereof; and Cyc represents a cyclic aliphatic moiety, aromatic moiety, aliphatic heterocyclic moiety, or aromatic heterocyclic moiety, each of said moieties optionally substituted with one or more groups which do not interfere with binding to an antibody or antibody fragment; with the proviso that when s, t, m, r, and n are 0, then R¹ is other than carboxyl; their pharmaceutically acceptable salts, their conjugates and the use thereof for radioimmunotherapy is disclosed.



patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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Jackson, TX 77566 (US). **GULYAS, Gyongyi** [US/US];
305 Timbercreek Drive, Lake Jackson, TX 77566 (US).

(21) International Application Number: PCT/US01/05927

(74) Agent: **KARADZIC, Dragan, J.**; The Dow Chemical
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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CZ, DE,
DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,
ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT,
LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ,
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KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant and

(72) Inventor: **MA, Dangshe** [US/US]; 13011 Twinbrook
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Published:

— without international search report and to be republished
upon receipt of that report

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(US). **FRANK, R., Keith** [US/US]; 213 Pansy Path, Lake

*For two-letter codes and other abbreviations, refer to the "Guid-
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(57) Abstract: Actinium-225 (²²⁵Ac) complexes with functionalized chelants of the formula (I) wherein: each Q is independently hydrogen or (CHR⁵)_nCO₂R; Q¹ is hydrogen or (CHR⁵)_wCO₂R; each R independently is hydrogen, benzyl or C₁-C₄ alkyl; with the proviso that at least two of the sum of Q and Q¹ must be other than hydrogen; each R⁵ independently is hydrogen; C₁-C₄ alkyl or (C₁-C₂ alkyl)phenyl; X and Y are each independently hydrogen or may be taken with an adjacent X and Y to form an additional carbon-carbon bond; n is 0 or 1; m is an integer from 0 to 10 inclusive; p is 1 or 2; r is 0 or 1; w is 0 or 1; with the proviso that n is only 1 when X and/or Y form an additional carbon to carbon bond, and the sum of r and w is 0 or 1; L is a linker/spacer group covalently bonded to, and replaces one hydrogen atom of one of the carbon atoms to which it is joined, said linker/spacer group being represented by the formula (1) wherein s is an integer of 0 or 1; t is an integer of 0 to 20 inclusive; R¹ is an electrophilic or nucleophilic moiety which allows for covalent attachment to an antibody or fragment thereof, or synthetic linker which can be attached to an antibody or fragment thereof, or precursor thereof; and Cyc represents a cyclic aliphatic moiety, aromatic moiety, aliphatic heterocyclic moiety, or aromatic heterocyclic moiety, each of said moieties optionally substituted with one or more groups which do not interfere with binding to an antibody or antibody fragment; with the proviso that when s, t, m, r, and n are 0, then R¹ is other than carboxyl; their pharmaceutically acceptable salts, their conjugates and the use thereof for radioimmunotherapy is disclosed.

WO 01/66155 A2

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REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

1

For receiving Office use only

International Application No. **PCT/US. 01/05927**

International Filing Date

(23.02.01)
23 FEB 2001**PCT INTERNATIONAL APPLICATION RO/US**

Name of Receiving Office and "PCT International Application"

Applicant's or Agent's file reference

60364A

Box No. I TITLE OF INVENTION

ACTINIUM-225 COMPLEXES AND CONJUGATES FOR RADIOIMMUNOTHERAPY

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Teleprinter No.

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US

State (that is, country) of residence:

US

This person is applicant for the purposes of:

☐

all designated States

☐

all designated States except the United States of America

☒

the United States of America only

☐

the States indicated in the Supplemental Box

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Bronx, New York 10471
United States of America**

This person is:

☐

applicant only

☒

applicant and inventor

☐

inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

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State (that is, country) of residence:

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☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☒ agent☐

common representative

Name and address:

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United States of America**

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Corresponds to: Form PCT/RO/101 (first sheet) (January 2001)

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If none of the following sub-boxes is used, this sheet is not to be included in the request.			
Name and address: SCHEINBERG, David A. 325 Central Park West New York, New York 10025 United States of America		This person is: <input type="checkbox"/> applicant only <input checked="" type="checkbox"/> applicant and inventor <input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)	
State (that is, country) of nationality: US		State (that is, country) of residence: US	
This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box			
Name and address: SIMON, Jaime Route 1, Box 199-A Angleton, Texas 77515 United States of America		This person is: <input type="checkbox"/> applicant only <input checked="" type="checkbox"/> applicant and inventor <input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)	
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This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box			
Name and address: KIEFER, Garry E. 114 Juniper Street Lake Jackson, Texas 77566 United States of America		This person is: <input type="checkbox"/> applicant only <input checked="" type="checkbox"/> applicant and inventor <input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)	
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This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box			
Name and address: FRANK, R. Keith 213 Pansy Path Lake Jackson, Texas 77566 United States of America		This person is: <input type="checkbox"/> applicant only <input checked="" type="checkbox"/> applicant and inventor <input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)	
State (that is, country) of nationality: US		State (that is, country) of residence: US	
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Name and address: GULYAS, Gyongyi 305 Timbercreek Drive Lake Jackson, Texas 77566 United States of America		This person is: <input type="checkbox"/> applicant only <input checked="" type="checkbox"/> applicant and inventor <input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)	
State (that is, country) of nationality: US		State (that is, country) of residence: US	
This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box			
Name and address:		This person is: <input type="checkbox"/> applicant only <input type="checkbox"/> applicant and inventor <input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)	
State (that is, country) of nationality:		State (that is, country) of residence:	
This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box			
Name and address:		This person is: <input type="checkbox"/> applicant only <input type="checkbox"/> applicant and inventor <input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)	
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Name and address:		This person is: <input type="checkbox"/> applicant only <input type="checkbox"/> applicant and inventor <input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)	
State (that is, country) of nationality:		State (that is, country) of residence:	
This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box			
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This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box			
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- ☒ EP European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
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- | | |
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| <input checked="" type="checkbox"/> AE United Arab Emirates | <input checked="" type="checkbox"/> LC Saint Lucia |
| <input checked="" type="checkbox"/> AL Albania | <input checked="" type="checkbox"/> LK Sri Lanka |
| <input checked="" type="checkbox"/> AG Antigua & Barbuda | <input checked="" type="checkbox"/> LR Liberia |
| <input checked="" type="checkbox"/> AM Armenia | <input checked="" type="checkbox"/> LS Lesotho |
| <input checked="" type="checkbox"/> AT Austria | <input checked="" type="checkbox"/> LT Lithuania |
| <input checked="" type="checkbox"/> AU Australia | <input checked="" type="checkbox"/> LU Luxembourg |
| <input checked="" type="checkbox"/> AZ Azerbaijan | <input checked="" type="checkbox"/> LV Latvia |
| <input checked="" type="checkbox"/> BA Bosnia and Herzegovina | <input checked="" type="checkbox"/> MA Morocco |
| <input checked="" type="checkbox"/> BB Barbados | <input checked="" type="checkbox"/> MD Republic of Moldova |
| <input checked="" type="checkbox"/> BG Bulgaria | <input checked="" type="checkbox"/> MG Madagascar |
| <input checked="" type="checkbox"/> BR Brazil | <input checked="" type="checkbox"/> MK The former Yugoslav Republic of Macedonia |
| <input checked="" type="checkbox"/> BY Belarus | <input checked="" type="checkbox"/> MN Mongolia |
| <input checked="" type="checkbox"/> BZ Belize | <input checked="" type="checkbox"/> MW Malawi |
| <input checked="" type="checkbox"/> CA Canada | <input checked="" type="checkbox"/> MX Mexico |
| <input checked="" type="checkbox"/> CH and LI Switzerland and Liechtenstein | <input checked="" type="checkbox"/> MZ Mozambique |
| <input checked="" type="checkbox"/> CN China | <input checked="" type="checkbox"/> NO Norway |
| <input checked="" type="checkbox"/> CR Costa Rica | <input checked="" type="checkbox"/> NZ New Zealand |
| <input type="checkbox"/> CU Cuba | <input checked="" type="checkbox"/> PL Poland |
| <input checked="" type="checkbox"/> CZ Czech Republic | <input checked="" type="checkbox"/> PT Portugal |
| <input checked="" type="checkbox"/> DE Germany | <input checked="" type="checkbox"/> RO Romania |
| <input checked="" type="checkbox"/> DK Denmark | <input checked="" type="checkbox"/> RU Russian Federation |
| <input checked="" type="checkbox"/> DM Dominica | <input checked="" type="checkbox"/> SD Sudan |
| <input checked="" type="checkbox"/> DZ Algeria | <input checked="" type="checkbox"/> SE Sweden |
| <input checked="" type="checkbox"/> EE Estonia | <input checked="" type="checkbox"/> SG Singapore |
| <input checked="" type="checkbox"/> ES Spain | <input checked="" type="checkbox"/> SI Slovenia |
| <input checked="" type="checkbox"/> FI Finland | <input checked="" type="checkbox"/> SK Slovakia |
| <input checked="" type="checkbox"/> GB United Kingdom | <input checked="" type="checkbox"/> SL Sierra Leone |
| <input checked="" type="checkbox"/> GD Grenada | <input checked="" type="checkbox"/> TJ Tajikistan |
| <input checked="" type="checkbox"/> GE Georgia | <input checked="" type="checkbox"/> TM Turkmenistan |
| <input checked="" type="checkbox"/> GH Ghana | <input checked="" type="checkbox"/> TR Turkey |
| <input checked="" type="checkbox"/> GM Gambia | <input checked="" type="checkbox"/> TT Trinidad and Tobago |
| <input checked="" type="checkbox"/> HR Croatia | <input checked="" type="checkbox"/> TZ United Republic of Tanzania |
| <input checked="" type="checkbox"/> HU Hungary | <input checked="" type="checkbox"/> UA Ukraine |
| <input checked="" type="checkbox"/> ID Indonesia | <input checked="" type="checkbox"/> UG Uganda |
| <input checked="" type="checkbox"/> IL Israel | <input checked="" type="checkbox"/> US United States of America |
| <input checked="" type="checkbox"/> IN India | <input checked="" type="checkbox"/> UZ Uzbekistan |
| <input checked="" type="checkbox"/> IS Iceland | <input type="checkbox"/> VN Viet Nam |
| <input checked="" type="checkbox"/> JP Japan | <input checked="" type="checkbox"/> YU Yugoslavia |
| <input checked="" type="checkbox"/> KE Kenya | <input checked="" type="checkbox"/> ZA South Africa |
| <input checked="" type="checkbox"/> KG Kyrgyzstan | <input checked="" type="checkbox"/> ZW Zimbabwe |
| <input type="checkbox"/> KP Democratic People's Republic of Korea | |
| <input checked="" type="checkbox"/> KR Republic of Korea | |
| <input checked="" type="checkbox"/> KZ Kazakhstan | |

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Box No. VI PRIORITY CLAIM <input type="checkbox"/> Further priority claims are indicated in the Supplemental Box.				
Filing date of earlier application (day/month/year)	Number of earlier application	national application: country	regional application:* regional Office	international application: receiving Office
item (1) 25 February 2000 (25.02.00)	60/185,220	US		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): (1)

* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY		
Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):	Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):	
ISA / EP	Date (day/month/year)	Number Country (or regional Office)

Box No. VIII CHECK LIST; LANGUAGE OF FILING	
This international application contains the following number of sheets:	This international application is accompanied by the item(s) marked below:
request : 5	1. <input checked="" type="checkbox"/> fee calculation sheet
description (excluding sequence listing part) : 23	2. <input type="checkbox"/> separate signed power of attorney
claims : 12	3. <input type="checkbox"/> copy of general power of attorney; reference number, if any:
abstract : 2	4. <input type="checkbox"/> statement explaining lack of signature
drawings : 0	5. <input type="checkbox"/> priority document(s) identified in Box No. VI as item(s):
sequence listing part of description : _____	6. <input type="checkbox"/> translation of international application into (language):
Total number of sheets : 42	7. <input type="checkbox"/> separate indications concerning deposited microorganisms or other biological material
	8. <input type="checkbox"/> nucleotide and/or amino acid sequence listing in computer readable form
	9. <input checked="" type="checkbox"/> other (specify): cover letter to USRO; Return Postcard

Figure of the drawings which should accompany the abstract:	Language of filing of the international application: English
---	---

Box No. IX SIGNATURE OF APPLICANT OR AGENT
MA, Dangshe, et al By: <u>Dragan J. Karadzic</u> Dragan J. Karadzic

1. Date of actual receipt of the purported international application: JC03 Rec'd PCT/PTO 23 FEB 2001	2. Drawings: <input type="checkbox"/> received: <input type="checkbox"/> not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): EP	6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid.

Date of receipt of the record copy by the International Bureau:

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/05927

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K51/04 A61K51/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EMBASE, BIOSIS, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 428 154 A (MAEGERSTAEDT MICHAEL A ET AL) 27 June 1995 (1995-06-27) claims	1
X	WO 99 30745 A (GOVINDAN SERENGULAM V ;HANSEN HANS (US); GRIFFITHS GARY L (US); IM) 24 June 1999 (1999-06-24) claims	1-20



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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Date of the actual completion of the international search

25 March 2002

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INTERNATIONAL SEARCH REPORT

International Application No.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SCHEINBERG, DAVID A. ET AL: "Clinical application of targeted alpha particles for cancer therapy" retrieved from STN Database accession no. 1998:141327 XP002194098 abstract & BOOK OF ABSTRACTS, 215TH ACS NATIONAL MEETING, DALLAS, MARCH 29-APRIL 2 (1998), NUCL-087 PUBLISHER: AMERICAN CHEMICAL SOCIETY, WASHINGTON, D. C.,</p>	1-20
P,X	<p>WO 00 59896 A (US HEALTH ;DEAL KIM (US); BRECHBIEL MARTIN W (US)) 12 October 2000 (2000-10-12) claims</p>	1
P,X	<p>MCDEVITT, M. R. (1) ET AL: "A novel alpha particle emitting 225Ac labeled anti-CD33 antibody construct: Synthesis and in vitro evaluation of biochemistry, potency, specificity and mechanism of cell death." JOURNAL OF NUCLEAR MEDICINE, (MAY, 2000) VOL. 41, NO. 5 SUPPL., PP. 30P. PRINT. MEETING INFO.: 47TH ANNUAL MEETING OF THE SOCIETY OF NUCLEAR MEDICINE ST. LOUIS, MISSOURI, USA JUNE 03-07, 2000 SOCIETY OF NUCLEAR MEDICINE., XP002194097 No116 page 30P</p>	1
E	<p>WO 02 05859 A (COCKBAIN JULIAN ;LARSEN ROY H (NO); ANTICANCER THERAPEUTIC INV S A) 24 January 2002 (2002-01-24) claims</p>	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/05927

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